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Breast Cancer

Use of Tamoxifen Before and During Pregnancy

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ABSTRACT

For premenopausal patients with receptor-positive early breast cancer, administration of tamoxifen for 5 years constitutes the main adjuvant endocrine therapy. During pregnancy, tamoxifen and its metabolites interact with rapidly growing and developing embryonic or fetal tissues.

Information about tamoxifen and pregnancy was gathered by searching PubMed. In addition, we had access to the records of the pharmaceutical company AstraZeneca. Because these observations are retrospective and other therapies and diagnostic measures are possible confounders, a causal relationship was not established between tamoxifen treatment and pregnancy outcome.

The records from AstraZeneca documented three live births with congenital anomalies and four live births without congenital anomalies related to tamoxifen treatment before pregnancy. Tamoxifen therapy during pregnancy resulted in 16 live births with congenital malformations and a total of 122 live births without malformations. The 122 live births without malformations included 85 patients from a prevention trial that did not record a single anomaly, whereas the AstraZeneca Safety Database alone reported 11 babies with congenital malformations of 44 live births. Additionally, there were: 12 spontaneous abortions, 17 terminations of pregnancy without known fetal defects, six terminations of pregnancy with fetal defects, one stillbirth without fetal defects, two stillbirths with fetal defects, and 57 unknown outcomes.

The relatively high frequency of severe congenital abnormalities indicates that reliable birth control during tamoxifen treatment is mandatory. After tamoxifen use, a washout period of 2 months is advisable based on the known half-life of tamoxifen. In case of an inadvertent pregnancy, risks and options should be discussed. ***The Oncologist*** 2011;16:1547–1551

INTRODUCTION

Breast cancer is the most common malignancy affecting women of reproductive age, with 10% of cases diagnosed before the age of 40. Fortunately, up to 60% of these patients can be successfully treated by a combination of early diagnosis, surgery, and adjuvant systemic therapy [1]. Indeed, women with a history of breast cancer now constitute the largest group in the cancer survivor community. For premenopausal patients with receptor-positive early disease, the main adjuvant endocrine therapy is the administration of tamoxifen for 5 years [2, 3].

Because of the high incidence of breast cancer, the increasing disease-free survival time, and the current trend toward postponing childbirth, oncologists will increasingly be confronted with patients treated with tamoxifen who desire to become pregnant or who unexpectedly become pregnant during tamoxifen treatment. The metabolism and action of tamoxifen are complex. During pregnancy, tamoxifen and its metabolites interact with rapidly growing and developing embryonic and fetal tissues. Discussion of the possible teratogenic and fetal adverse effects of tamoxifen is mandatory when counseling these women.

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TAMOXIFEN

Tamoxifen is a nonsteroidal selective estrogen receptor modulator with a complex metabolism, various mechanisms of actions at different levels, and a long half-life. Originally, it was developed as a contraceptive agent, but it was found to stimulate follicle growth and was proven to be as effective as clomiphene for the induction of ovulation in patients with anovulatory infertility. However, the issue of teratogenicity limited its use for this indication. Because of its strong antiestrogenic actions on breast cancer cells, tamoxifen became an important part of the adjuvant therapy for early-stage, hormone-sensitive breast cancer [2, 3]. Furthermore, it has been shown to be effective for chemoprevention of breast cancer [4].

The cellular response to tamoxifen occurs through competition between tamoxifen and endogenous estrogens for binding sites on the estrogen receptor (ER). Estrogen (E) activates two signaling pathways on ER binding: a genomic and a less important nongenomic (membrane-initiated) signaling pathway [5]. In the genomic pathway, DNA binding of the bound ER–E complex results in a response that alters gene transcription and translation, whereas the nongenomic pathway involves the stimulation of membrane-bound receptor tyrosine kinases. In the genomic pathway, the resulting response, stimulatory or inhibitory, is cell specific as a result of the presence of specific coactivators and corepressors. Although inhibitory effects are observed in the breast, the higher incidence of endometrial cancer among tamoxifen users also demonstrates stimulatory effects on the endometrium.

The metabolism of tamoxifen is complex. It is well absorbed orally and has a protein binding rate of 99%. Metabolism is by the cytochrome P450 (CYP) system found in liver microsomes [6, 7]. Some of the metabolites of tamoxifen exhibit a stronger antiestrogenic effect on breast cancer cells than tamoxifen itself. The major pathway is the N-demethylation of tamoxifen by the enzymes CYP3A4 and CYP3A5, resulting in the formation of N-desmethyltamoxifen. N-desmethyltamoxifen can be hydroxylated by CYP2D6 into endoxifen, a very potent metabolite in terms of antiestrogenic activity with high plasma levels. Another metabolic pathway is the hydroxylation of tamoxifen into 4-OH-tamoxifen by CYP2D6. The antiestrogenic activity of 4-OH-tamoxifen is approximately 30- to 100-fold higher than that of tamoxifen and comparable with that of endoxifen; however, plasma concentrations of 4-OH-tamoxifen are about six times lower than those of endoxifen. Endoxifen and 4-OH-tamoxifen have high binding affinities to ERs, antiproliferative activity, and inhibitory effects on the expression of typical estrogen-related genes [8]. Pregnancy is characterized by growth and development, both of which are tightly linked to transcription and translation in strict time frames. Knowing the potent actions of tamoxifen and its metabolites, it is evident that there is a strong concern about the use of tamoxifen during pregnancy.

Patterson et al. [9] determined the half-life of tamoxifen and the major metabolite N-desmethyltamoxifen. After the initiation of tamoxifen therapy, steady-state concentrations were achieved after about 4 weeks for tamoxifen, indicating an elimination half-life of 7 days. N-desmethyltamoxifen reached steady-state concentrations after about 8 weeks; the half-life was determined to be approximately 14 days [9]. MacCallum et al. [10] measured the concentrations of tamoxifen and its major metabolites. Administration of 20 mg tamoxifen daily, the standard dose, for at least 3 months resulted in an average plasma concentration of 115 ng/mL for tamoxifen, 235 ng/mL for N-desmethyltamoxifen, and 67 ng/mL for 4-OH-tamoxifen, although large individual variations were observed. Furthermore, concentrations in tumor tissue were roughly two to two and a half times higher than those in plasma [10]. Tamoxifen metabolites are secreted in bile and undergo enterohepatic circulation. Fecal excretion is the primary route of elimination. The effects of age, gender, and race on the pharmacokinetics of tamoxifen have not been determined, nor have the effects of reduced liver function. The rather long half-life of tamoxifen has its consequences for practical advice. The product information provided by the pharmaceutical company AstraZeneca Pharmaceuticals (Wilmington, DE) advises informing women of the potential risks to the fetus should they become pregnant while taking tamoxifen or within 2 months of cessation of therapy.

TAMOXIFEN AND PREGNANCY

Studies in animals have demonstrated adverse effects of tamoxifen on the fetus and fetal loss. Epithelial changes similar to those seen after administration of diethylstilbestrol (DES) or clomiphene citrate have been reported in mice and rats exposed to tamoxifen [11]. In particular, vaginal adenosis was observed, which is comparable with the changes seen in young women exposed to DES in utero. DES-exposed women have an inherent risk for developing clear cell carcinoma of the vagina or cervix of one in 1,000. However, it appears that the effects of tamoxifen on these aspects of development are species specific.

In this study, information regarding exposure in humans to tamoxifen before and during pregnancy was gathered by tracking cases using PubMed (U.S. National Library of Medicine, National Institutes of Health), but the majority of the information was provided by the records of the safety database of AstraZeneca. Those observations are described in narratives and mostly consist of one or a couple of lines with essential information. The records were edited by the authors with the aim to present an overview that was as complete as possible but that was also comprehensible. One caveat of the cases presented here is the limitation of retrospective observations. Furthermore, other therapies and diagnostic measures are possible confounders; thus, a causal relationship has not been established between treatment with tamoxifen and pregnancy outcome.

RESULTS

The effects of tamoxifen before conception are shown in Table 1. There are no details about the exact usage or discontinuation of tamoxifen in relation to conception. Of 11 pregnancies, there were three live births with various congenital malformations, one stillbirth with fetal defects, and one spontaneous

Table 1. Effects of tamoxifen before conception

Source	*n* of patients	Tamoxifen exposure	Outcome
Astra Zeneca Safety Database	11	Before conception	Three live births with congenital anomalies: one baby of a twin pregnancy with multiple malformations, one anorectal anomaly, one diaphragmatic hernia (died after 19 hours). One stillbirth with fetal defects; one spontaneous abortion; four live births without congenital anomaly; one elective termination (no fetal defects or unknown); one unknown

abortion reported. In contrast, four live births without congenital anomalies were also reported along with one elective termination of pregnancy and one unknown outcome.

The effects of tamoxifen during pregnancy (Table 2) are described by several case reports [12–17], a trial on breast cancer prevention [18], and the records provided by AstraZeneca. A case report by Tewari et al. [12] describes an infant born with ambiguous genitalia. Cullins et al. [13] discussed a child with Goldenhar's syndrome, characterized by hemifacial microsomia, microtia, and periauricular skin tags. However, a confounding history of maternal cocaine and marijuana use and exposure to technetium medronate were also present in that case [13]. Berger and Clericuzio described a Pierre Robin sequence associated with first trimester fetal tamoxifen exposure [14]. In contrast, three other case reports mention a total of four live births without congenital anomalies [15–17]. In 1993, Clark published an abstract in *The Lancet* about 85 women who became pregnant while receiving prophylactic tamoxifen as part of a trial in healthy women at high risk for breast cancer. No fetal abnormalities were observed but the author did not indicate the duration of tamoxifen treatment during pregnancy [18]. Two of the participants did have spontaneous abortions, which were reported in the narratives of the AstraZeneca Safety Database. However, it is unclear whether these participants were treated with tamoxifen or placebo.

The AstraZeneca Safety Database documents 136 pregnancies, one of which was reported previously [13]. There were: 10 live births with congenital anomalies, one stillbirth with fetal defects, and six terminations with fetal defects, but also 33 live births without congenital anomalies, one stillbirth without fetal defects, 16 terminations of pregnancy without fetal defects or unknown, 11 spontaneous abortions, one ectopic pregnancy, and 56 unknown outcomes. In 2004, Barthelmes and Gateley reviewed tamoxifen exposure during pregnancy. The cases discussed above from the literature, including a preliminary total of 50 pregnancies recorded by AstraZeneca, were presented in that publication [19]. This publication is not included in Table 2 because it assessed pregnancies that have been already listed.

In summary, taking all these figures together, there were 16 live births with congenital malformations and a total of 122 live births without malformations. The 122 live births without malformations included 85 patients of the prevention trial without a single recorded anomaly, whereas the AstraZeneca Safety Database alone showed 11 babies with congenital malformations of 44 live births. In addition, there were 12 spontaneous abortions, 17 terminations of pregnancy without known fetal defects, six terminations of pregnancy with fetal defects, one stillbirth without fetal defects, two stillbirths with fetal defects, and 57 unknown outcomes.

Discussion

These findings relating to tamoxifen use during or before pregnancy are, for obvious reasons, not based on well-controlled studies but depend on case reports and reports documented in the AstraZeneca Safety Database. The observations are retrospective and other therapies and diagnostic measures are possible confounders. Therefore, a causal relationship has not been established between treatment with tamoxifen and pregnancy outcome. Follow-up data on the babies are not available, and are also not reported in the AstraZeneca Safety Database.

The relatively high frequency of severe congenital abnormalities indicates that it is prudent to stop tamoxifen before pregnancy. The AstraZeneca Safety Database registered 11 babies with congenital malformations of 44 live births, which is one live birth with malformations for every four. In fact, the number of malformations was even higher, because there were six terminations of pregnancy and two stillbirths with fetal defects, compared with 17 terminations of pregnancy without known fetal defects and one stillbirth without fetal defects, which is nearly a rate of one in three births. The report of 85 women who became pregnant while receiving prophylactic tamoxifen [18] is in sharp contrast with these observations. However, no detailed information about the intake of tamoxifen was provided, whereas the cases reported to AstraZeneca are better documented. Another aspect is the number of spontaneous abortions or stillbirths reported, but no causal link with tamoxifen use has been established. The miscarriage rate is within normal limits.

Teratogenicity during the first trimester of pregnancy has always been of particular interest. The data support this concern about teratogenicity, but malformations were also reported following tamoxifen treatment after the first trimester. Therefore, tamoxifen should not be taken at any time during pregnancy.

No specific congenital anomaly has been associated with the use of tamoxifen during pregnancy. The existing literature and the AstraZeneca Safety Database did not show

Table 2. Effects of tamoxifen during pregnancy

Source	*n* of patients	Tamoxifen exposure	Outcome
Tewari et al. [12]	1	Until 20 wks	One live birth with congenital anomaly: ambiguous genitalia with clitoris hypertrophia
Cullins et al. [13]	1	Until 26 wks	One live birth with congenital anomaly: Goldenhar's syndrome. Note: marijuana-cocaine inhalation during first 6 wks of pregnancy and bone scan
Berger and Clericuzio [14]	1	First trimester	One live birth with congenital anomaly: Pierre-Robin sequence with severe micrognathia and cleft palate
Öksüzoglu et al. [15]	1	First trimester	One live birth without congenital anomaly
Koizumi and Aono [16]	2	First trimester	Two live births without congenital anomaly
Isaacs et al. [17]	1	After first trimester	One live birth without congenital anomaly
Clark [18]	85	Unknown	No fetal abnormalities
Astra Zeneca Safety Database	37	First trimester	Two live births with congenital anomalies: one girl delivered at 29 wks with XXX chromosomes and also a phallic-like clitoris and huge labia, and one idiopathic chylothorax. Two elective terminations with fetal defects; six spontaneous abortions; six live births without congenital anomalies; four elective terminations (no fetal defects or unknown); 17 unknown
Astra Zeneca Safety Database	15	After first trimester	Two live births with congenital anomaly: one congenital hand malformation, and one vaginal adenoma at 2.5 years. One elective termination with fetal defects; eight live births without congenital anomaly; one elective termination (no fetal defects or unknown); three unknown
Astra Zeneca Safety Database	10	During all pregnancy	One live birth with congenital anomaly: one Goldenhar's syndrome (Cullins'report). Eight live births without congenital anomalies; one elective termination (no fetal defects or unknown)
Astra Zeneca Safety Database	74	Unknown	Six live births with congenital anomaly: one cleft palate, one ear malformation, one trisomy 21, one with small degree of labial fusion, one with craniofacial defects, one slight clitoral hypertrophy. One stillbirth with fetal defects; three elective terminations with fetal defects; one stillbirth without fetal defects; five spontaneous abortions; one ectopic pregnancy; 11 live births without congenital anomaly; 10 elective terminations (no fetal defects or unknown); 36 unknown

that in utero exposure to tamoxifen causes vaginal adenosis or clear cell adenocarcinoma of the vagina or cervix in young women. However, the value of this evidence is limited because only a small number of young women have been exposed to tamoxifen in utero, and even a smaller number have been followed for a long enough period [11]. Children who have been exposed to tamoxifen during pregnancy are advised to have long-term follow-up [15, 20].

Conclusions

The relatively high frequency of severe congenital abnormalities indicates that a reliable birth control method is mandatory during tamoxifen treatment. The half-life of tamoxifen and its metabolites is rather long. The patient should be informed about a washout period of 2 months before conceiving. If an inadvertent pregnancy occurs, the potential risks for the fetus and newborn should be discussed with the patient, along with the possible options.

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Geert Braems and Hannelore Denys contributed equally.

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